UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BRISTOL-MYERS SQUIBB CO., E. R. SQUIBB & SONS L.L.C., ONO PHARMACEUTICAL CO., LTD., DR. TASUKU HONJO, and DANA-FARBER CANCER INSTITUTE, INC.,	)	
Plaintiffs,	)	C.A. No. _____
v.	)	**JURY TRIAL DEMANDED**
ASTRAZENECA PHARMACEUTICALS LP and ASTRAZENECA UK LTD.,	)	
Defendants.	)	

COMPLAINT

Plaintiffs Bristol-Myers Squibb Co. ("BMS"), E. R. Squibb & Sons L.L.C. ("Squibb"), Ono Pharmaceutical Co., Ltd. ("Ono"), Dr. Tasuku Honjo, and Dana-Farber Cancer Institute, Inc. ("DFCI") (collectively "Plaintiffs"), for their complaint for patent infringement against Defendants AstraZeneca Pharmaceuticals LP and AstraZeneca UK Ltd. (collectively, "Defendants" or "AstraZeneca"), hereby allege as follows:

INTRODUCTION

1. This case relates to groundbreaking methods of treating cancer that revolutionized the field of medicine. The claimed methods of treatment, called "immunotherapy," work by manipulating a patient's immune system to trigger an anti-cancer response. In particular, the methods of treatment in this case relate to using an antibody to inhibit the interaction between PD-1 and PD-L1 to treat cancer in patients. The discovery that this pathway could be blocked to treat cancer resulted in the award of the Nobel Prize in Physiology or Medicine in 2018 to

plaintiff-inventor Dr. Tasuku Honjo. The inventions at issue here, which are described and claimed in U.S. Patent No. 9,402,899 ("the '899 patent"), cover those Nobel Prize winning methods of treating cancer.

2. In addition to Dr. Honjo, the claimed methods of treating cancer were discovered through the work of Dr. Gordon Freeman at DFCI, Dr. Clive Wood at an entity formerly called Genetics Institute, Drs. Nagahiro Minato and Yoshiko Iwai at Kyoto University, and Dr. Shiro Shibayama at Ono.

3. DFCI is a non-profit corporation committed to providing adults and children suffering from cancer with the best treatments available. As an affiliate of Harvard Medical School and a National Cancer Institute-designated Comprehensive Cancer Center, DFCI's commitment includes developing innovative future therapies through cutting-edge research, including supporting the work of its scientists like Dr. Freeman.

4. BMS, Squibb, and Ono are engaged in the business of creating, developing, and bringing to market pharmaceutical products to help patients prevail against serious diseases. For almost two decades, BMS, Squibb, and Ono have partnered to develop and commercialize the novel methods of treatment discovered by Dr. Honjo and his co-inventors. Despite initially facing a great deal of skepticism, the methods of treatment have been transformative in the field of cancer therapy.

Cancer and Immunotherapy

5. According to the United States Centers for Disease Control and Prevention, more than 1.7 million people in the United States are diagnosed with cancer each year (https://www.cdc.gov/chronicdisease/resources/publications/factsheets/cancer.htm). Cancer is a disease that results from the uncontrolled proliferation of cells that were once normal but have

transformed into cancerous cells. Although the human immune system has the potential to eliminate cancerous cells, cancer cells have the ability to "turn off" or evade the immune system, allowing the cancer cells to grow unchecked. Tumor growth and tumor metastasis can lead to devastating disease, and possibly death. Cancer treatments therefore seek to decrease tumor growth and metastasis.

6. The human immune system is formed of organs, specialized cells, and substances that protect individuals from infections and disease. T cells are one class of specialized cells that play an important role in the human immune system. One major function of T cells is to destroy pathogens or malignant cells, and to do that the T cell must distinguish healthy cells from infected or malignant cells through the activation or deactivation of various receptors on the T cell surface. One of the receptors that T cells express on their surface is a protein called programmed death-1 receptor ("PD-1"). PD-1 functions as a checkpoint on the immune system that can downregulate T cell activity to prevent an overactive immune response. To activate its inhibitory function, PD-1 must bind to one of its ligands. Programmed death-ligand 1 ("PD-L1") is one of these ligands.

7. Numerous forms of cancer cells and/or antigen-presenting cells, such as activated monocytes and dendritic cells, express PD-L1 on their cell surface, thereby exploiting PD-1's ability to downregulate the immune response. When PD-L1 on a cancer or antigen-presenting cell binds to PD-1 on immune cells, such as a T cell, it can result in the suppression of T cell migration, proliferation, and secretion of cytotoxic mediators. Cancer cells expressing PD-L1 use this pathway to prevent the immune system from eliminating those cancer cells.

Immunotherapy Treatments

8. The inventions of the '899 patent at issue here generally relate to treatments for cancer and enhancing immune responses by administering antibodies that bind to PD-L1 ("anti-PD-L1 antibodies"). The '899 patent demonstrated for the first time that anti-PD-L1 antibodies inhibit the interaction between PD-1 and PD-L1 and that by binding to PD-L1 and blocking its interaction with PD-1, the anti-PD-L1 antibodies act as checkpoint inhibitors that release the brakes on the immune system, freeing the immune cells to recognize, attack, and destroy cancer cells.

9. Dr. Honjo, Ono, and DFCI are the owners of the '899 patent; BMS and Squibb are exclusive licensees. Through their partnership, BMS, Squibb, and Ono developed and commercialized an antibody called nivolumab that recognizes and binds to PD-1 (an "anti-PD-1 antibody"). Nivolumab, which is sold under the trade name OPDIVO, put Dr. Honjo's and his co-inventors' breakthrough inventions into practice. It is the first antibody targeting the PD-1/PD-L1 pathway approved anywhere in the world for cancer treatment, and the first anti-PD-1 antibody approved in the United States for the treatment of lung cancer.

10. When nivolumab binds to PD-1, it prevents PD-1 from binding its ligands, e.g., PD-L1. Using nivolumab to block the interaction between PD-1 and its ligands enhances the T cell response generated by the patient's immune system.

11. After rigorous worldwide testing, on July 4, 2014, Japanese regulatory authorities approved nivolumab for the treatment of melanoma, a deadly form of skin cancer. On December 22, 2014, the FDA approved nivolumab for the treatment of advanced melanoma in the United States.

12. BMS, Squibb, and Ono have continued worldwide development of nivolumab for treatment of a broad range of cancers, including non-small cell lung cancer, urothelial carcinoma, renal cell carcinoma, head and neck cancer, malignant pleural mesothelioma, lymphoma, colorectal cancer, hepatocellular carcinomas, esophageal cancer, and gastric cancers. In Phase III clinical testing for lung cancer, patients with advanced lung cancer who received nivolumab showed superior overall survival (41% reduction in the risk of death) compared to those who received the standard of care chemotherapy agent docetaxol (https://news.bms.com/news/details/2015/FDA-Approves-Opdivo-nivolumab-for-the-Treatment-of-Patients-with-Previously-Treated-Metastatic-Squamous-Non-Small-Cell-Lung-Cancer/default.aspx). Based, at least in part, on these clinical results, on February 27, 2015, the FDA accepted a Biologics License Application ("BLA") for use of nivolumab to treat lung cancer. Just days later, on March 4, 2015, the FDA approved nivolumab for treatment of advanced non-small cell lung cancer in the United States. In Phase III clinical testing for urothelial carcinoma, median disease-free survival was nearly twice as long in patients who received nivolumab as compared to placebo (https://news.bms.com/news/details/2021/U.S.-Food-and-Drug-Administration-Approves-Opdivo-nivolumab-for-the-Adjuvant-Treatment-of-Patients-with-High-Risk-Urothelial-Carcinoma/default.aspx). On August 19, 2021, based at least in part on these clinical results, the FDA approved nivolumab to treat certain types of urothelial carcinoma. The clinical results and the FDA's approval of nivolumab for the treatment of various additional forms of cancer confirm that cancer treatments that target the PD-1/PD-L1 pathway, such as the claimed cancer treatments, can be used to save the lives of patients suffering from cancer.

13. AstraZeneca has long known about the inventions claimed in the '899 patent, but has never obtained a license. Instead, and in willful and deliberate disregard of Plaintiffs' intellectual property rights, AstraZeneca has chosen to exploit the inventions claimed in the '899 patent by making and selling a later-developed anti-PD-L1 antibody product, IMFINZI (durvalumab), which it markets for use in methods of treating cancer and for enhancing the immune response that infringe the claims of the '899 patent.

14. Since AstraZeneca's IMFINZI product directly competes against OPDIVO for use in the field of immunotherapy, and more specifically, for use in treating cancer in the PD-1/PD-L1 antibody field, Plaintiffs have suffered, and continue to suffer, substantial damages, including lost profits, as a result of AstraZeneca's willful infringement.

PARTIES

15. BMS is a corporation organized under the laws of the state of Delaware, with a principal place of business at Route 206 & Province Line Road, Princeton, New Jersey 08543. Squibb is a limited liability company organized and existing under the laws of the state of Delaware, with its principal place of business at Route 206 & Province Line Road, Princeton, New Jersey 08543. Ono is a corporation organized under the laws of Japan, with a place of business at 8-2 Kyutaromachi 1-chome, Chuo-ku, Osaka 541-8564, Japan. Tasuku Honjo is an individual with a place of business at Kyoto University, Graduate School of Medicine, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan. DFCI is a Massachusetts non-profit corporation with a place of business at 450 Brookline Avenue, Boston, Massachusetts 02215.

16. AstraZeneca Pharmaceuticals LP is a limited partnership organized under the laws of the State of Delaware, with its principal place of business at 1800 Concord Pike, Wilmington, Delaware 19803.

17. AstraZeneca UK Limited is a private limited company organized under the laws of England and Wales, with its registered office at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, United Kingdom, CB2 0AA.

18. AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited are in the business of manufacturing, marketing, distributing, offering for sale, and selling drug products that are distributed and sold throughout the United States, including in Delaware.

19. AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited are sophisticated pharmaceutical companies. On information and belief, AstraZeneca relies on and actively seeks patent protection for its products. On information and belief, AstraZeneca recognizes the importance of intellectual property rights in protecting valuable inventions, and, indeed, it regularly enforces its patents and other intellectual property rights against others.

JURISDICTION AND VENUE

20. This is an action for patent infringement arising under the Patent Laws of the United States, 35 U.S.C. §§ 271 *et seq*.

21. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

22. This Court has personal jurisdiction over AstraZeneca Pharmaceuticals LP because it is a Delaware entity located and incorporated in Delaware.

23. This Court has jurisdiction over AstraZeneca UK Limited because, *inter alia*, its subsidiary and agent, AstraZeneca Pharmaceuticals LP, is incorporated in Delaware and, upon information and belief, markets and sells IMFINZI in Delaware as AstraZeneca UK Limited's authorized agent and under AstraZeneca UK Limited's direction and control.

24. This Court further has personal jurisdiction over Defendant AstraZeneca UK Limited because at least one provision of the Delaware long-arm statute, 10 Del. C. § 3104(c), is satisfied. On information and belief, Defendant AstraZeneca UK Limited satisfies at least § 3104(c)(1) ("[t]ransacts any business or performs any character of work or service in the State"), § 3104(c)(2) ("[c]ontracts to supply services or things in this State"), § 3104(c)(3) ("[c]auses tortious injury in the State by an act or omission in this State"), § 3104(c)(4) ("[c]auses tortious injury in the State or outside of the State by an act or omission outside the State if the person regularly does or solicits business, engages in any other persistent course of conduct in the State or derives substantial revenue from services, or things used or consumed in the State"), § 3104(c)(5) ("[h]as an interest in, uses or possesses real property in the State").

25. In the alternative, this Court has personal jurisdiction over Defendant AstraZeneca UK Limited because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (1) Plaintiffs' claims raise under federal law; (2) Defendant AstraZeneca UK Limited is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (3) Defendant AstraZeneca UK Limited has sufficient contacts with the United States as a whole, including but not limited to, preparing and submitting BLAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Defendant AstraZeneca UK Limited satisfies due process.

26. On information and belief, AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited are engaged in a single business activity of biopharmaceuticals and are not separated into multiple operating segments. On information and belief, the biopharmaceuticals business of AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited consists of the discovery and

development of products, which are then manufactured, marketed, and sold. On information and belief, all of these functional activities take place (and are managed) globally on a highly integrated basis. On information and belief, these individual functional areas are not managed separately.

27. On information and belief, AstraZeneca Pharmaceuticals LP and AstraZeneca UK Limited have consented to jurisdiction in Delaware in one or more prior cases arising out of the manufacture, use, offer for sale, sale and/or importation of pharmaceutical products, including cases AstraZeneca initiated as the plaintiff.

28. Venue is proper in this district under 28 U.S.C. §§ 1391(c) and 1400(b).

THE PATENT-IN-SUIT

29. On August 2, 2016, the United States Patent & Trademark Office ("USPTO") duly and legally issued the '899 patent, titled "Immunopotentiative Composition." A true and correct copy of the '899 patent is attached hereto as Exhibit 1.

30. The '899 patent issued from U.S. Application No. 14/245,692, filed on April 4, 2014, which is a divisional application of U.S. Application No. 12/959,307, filed on December 2, 2010 (now U.S. Pat. No. 8,728,474), which is a divisional application of U.S. Application No. 12/538,698, filed on August 10, 2009 (now U.S. Pat. No. 8,168,179), which is a divisional application of U.S. Application No. 10/519,925, filed on January 3, 2005 (now U.S. Pat. No. 7,595,048), which is a National Stage Entry of PCT/JP03/08420 filed on July 2, 2003, which claims priority based on Japanese Patent Application Nos. 2002-194491 and 2003-029846 filed on July 3, 2002 and February 6, 2003, respectively.

31. The claims of the '899 patent are generally directed to methods of treating cancer by administering an anti-PD-L1 monoclonal antibody that inhibits the interaction between PD-1 and PD-L1. By way of example, claim 1 of the '899 patent is:

> A method of treating a tumor in a human patient in need thereof comprising
>
> administering to the human an effective amount of an anti-PD-L1 monoclonal antibody that inhibits an interaction between PD-1 and PD-L1,
>
> wherein the anti-PD-L1 monoclonal antibody treats the tumor in the patient.

32. Dr. Tasuku Honjo is a co-inventor and original co-assignee of the '899 patent. Ono is an original co-assignee and exclusive licensor of BMS under the '899 patent. BMS and Squibb are each exclusive licensees of one or more exclusionary rights under the '899 patent.

33. BMS, Squibb, Ono, and Tasuku Honjo filed suit against AstraZeneca on July 26, 2017, and served AstraZeneca with that complaint no later than July 31, 2017. *See Bristol-Myers Squibb Co. v. AstraZeneca Pharms LP*, 17-cv-1028 (D. Del. filed July 26, 2017) (the "2017 Action"). That suit alleged that the use of IMFINZI infringed at least claims 1-7, 16, 19-24, 33, 36-38, 41, and 43-51 of the '899 patent. AstraZeneca answered that Complaint on October 4, 2017.

34. On May 17, 2019, a district court determined that Gordon Freeman and Clive Wood were co-inventors of the '899 patent. *Dana-Farber Cancer Institute, Inc. v. Ono Pharm. Co., Ltd.*, 15-cv-13443 (D. Mass. filed Sept. 25, 2015) (the "Inventorship Action"). The district court's decision in the Inventorship Action was affirmed on appeal on July 14, 2020 and the United States Supreme Court denied *certiorari* on May 24, 2021. DFCI is the owner of Gordon Freeman's rights under the '899 patent. Ono is the owner of Clive Wood's rights under the '899 patent.

35. After the district court's ruling in the Inventorship Action, the 2017 Action against AstraZeneca, which did not include DFCI, was dismissed without prejudice on June 13, 2019.

ASTRAZENECA'S IMFINZI PRODUCT

36. AstraZeneca UK Limited is the holder of BLA No. 761069 for IMFINZI. The active ingredient in AstraZeneca's IMFINZI product is the anti-PD-L1 antibody durvalumab. According to IMFINZI's label, durvalumab is a human IgG1κ monoclonal antibody that binds to human PD-L1 and blocks the interaction of PD-L1 with PD-1. Durvalumab interferes with the PD-L1/PD-1 mediated inhibition of the immune response in order to produce an anti-tumor immune response. IMFINZI's label also indicates that IMFINZI is manufactured for AstraZeneca Pharmaceuticals LP by AstraZeneca UK Limited. On information and belief, AstraZeneca Pharmaceuticals LP is marketing, using, distributing, offering for sale, selling, and importing IMFINZI in the United States as AstraZeneca UK Limited's authorized agent.

37. On or about May 1, 2017, AstraZeneca began marketing IMFINZI in the United States for the treatment of urothelial carcinoma, including locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy, and continues to do so today.

38. On or about February 16, 2018, AstraZeneca began marketing IMFINZI in the United States for the treatment of non-small cell lung cancer (NSCLC), including for unresectable Stage III NSCLC in patients whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy, and continues to do so today.

39. On or about March 27, 2020, AstraZeneca began marketing IMFINZI in the United States for extensive-stage small cell lung cancer (ES-SCLC), including in combination

with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with ES-SCLC, and continues to do so today.

40. On or about September 2, 2022, AstraZeneca began marketing IMFINZI in the United States for the treatment of biliary tract cancer (BTC), including in combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic BTC, and continues to do so today.

41. On or about October 21, 2022, AstraZeneca began marketing IMFINZI in the United States for the treatment of unresectable hepatocellular carcinoma (uHCC), including in combination with tremelimumab-actl for the treatment of adult patients with uHCC, and continues to do so today.

42. On or about November 10, 2022, AstraZeneca began marketing IMFINZI in the United States in combination with tremelimumab-actl and platinum-based chemotherapy, for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, and continues to do so today.

THE USE OF IMFINZI INFRINGES THE '899 PATENT

43. On information and belief, AstraZeneca has and is currently manufacturing, distributing, using, offering for sale, selling, and/or importing in the United States its IMFINZI antibody product to be prescribed and used for the treatment of cancer according to the IMFINZI prescribing information.

44. As described above, and according to the instructions in the prescribing information for IMFINZI, IMFINZI is used for treating a tumor in a human patient. IMFINZI is administered in an effective amount. The IMFINZI antibody (durvalumab) is an anti-PD-L1

monoclonal antibody that inhibits an interaction between PD-1 and PD-L1. When administered to a human patient with a tumor, the IMFINZI antibody treats the tumor in the patient.

45. On information and belief, IMFINZI has been and is currently being used according to the instructions in its prescribing information. The use of IMFINZI according to the instructions in its prescribing information infringes at least independent claim 1 of the '899 patent.

46. According to the instructions in the prescribing information for IMFINZI, "PD-L1 blockade with durvalumab led to . . . decreased tumor size in co-engrafted human tumor and immune cell xenograft mouse models." On information and belief, the use of IMFINZI according to the instructions in its prescribing information decreases tumor growth in human patients. Including for the reasons above, the use of IMFINZI according to the instructions in its prescribing information further infringes at least independent claim 19 of the '899 patent.

47. According to the instructions in the prescribing information for IMFINZI, IMFINZI is marketed to treat several types of metastatic cancer, including non-small cell lung cancer and biliary tract cancer. On information and belief, the use of IMFINZI according to the instructions in its prescribing information suppresses metastasis of tumor cells in human patients. Including for the reasons above, the use of IMFINZI according to the instructions in its prescribing information further infringes at least independent claim 36 of the '899 patent.

48. As described above, the prescribing information for IMFINZI describes durvalumab as a human antibody. The use of IMFINZI according to the instructions in the prescribing information therefore infringes at least claims 2, 20, and 43 of the '899 patent.

49. As described above, IMFINZI is and/or has been marketed by AstraZeneca to treat several types of cancers, including solid tumors like lung cancer, hepatocellular carcinoma,

urothelial carcinoma, and biliary tract cancer. The use of IMFINZI according to the instructions in the prescribing information therefore infringes at least claims 3, 21, and 37 of the '899 patent.

50. On information and belief, including for the reasons above, the administration of IMFINZI to patients is used to decrease tumor growth and/or to suppress the growth of tumor cells. The use of IMFINZI according to the instructions in the prescribing information therefore infringes at least claim 4 of the '899 patent.

51. On information and belief, including for the reasons above, the administration of IMFINZI to patients is used to suppress tumor metastasis. The use of IMFINZI according to the instructions in the prescribing information therefore infringes at least claims 5, and 22 of the '899 patent.

52. As described above, IMFINZI is and/or has been marketed by AstraZeneca to treat types of urothelial carcinoma, NSCLC, ES-SCLC, hepatocellular carcinoma, and biliary tract cancer. Urothelial carcinoma is a type of cancer that begins in urothelial cells, and can form tumors in organs in the urinary tract, including the bladder. Both NSCLC and ES-SCLC are types of cancer that form tumors in the lung. The '899 patent explains that lung cancer includes squamous carcinoma and adenocarcinoma, and bladder cancer includes squamous carcinoma. '899 patent at 11:25-35. The use of IMFINZI according to the instructions in the prescribing information therefore infringes at least claims 6-9, 12, 23-26, 29, 38-42, and 44-45 of the '899 patent.

53. According to the instructions in the prescribing information for IMFINZI, IMFINZI is administered systemically by intravenous infusion. The use of IMFINZI according to the instructions in the prescribing information therefore infringes at least claims 16 and 33 of the '899 patent.

54. As described above, the prescribing information for IMFINZI describes durvalumab as an IgG1 antibody. The use of IMFINZI according to the instructions in the prescribing information therefore infringes at least claims 46-51 of the '899 patent.

55. Thus, for the reasons described above, when medical professionals or others administer IMFINZI according to the instructions in the prescribing information, they directly infringe the '899 patent. On information and belief, AstraZeneca knows that IMFINZI has been and is currently being used according to the instructions in the prescribing information.

56. On information and belief, AstraZeneca has known about the '899 patent and AstraZeneca's infringement of the '899 patent since at least as early as August 2, 2016, when the '899 patent issued, but, if not, at least as of July 31, 2017 when it received a copy of the Complaint in the 2017 Action. In any event, for the reasons below, AstraZeneca knew of the '899 patent and AstraZeneca's infringement of the '899 Patent since at least before the filing of this Complaint.

57. AstraZeneca has had knowledge of the '899 patent since the '899 patent issued because EP1537878 ("EP878 patent"), a European counterpart to the '899 patent that discloses methods of treating tumors with anti-PD-L1 antibodies was included in an information disclosure statement filed on May 16, 2014, during prosecution of the application that led to AstraZeneca's U.S. Patent No. 8,779,108 (the "'108 patent"). The '108 patent describes the development of durvalumab, specifically claims durvalumab, and is assigned to MedImmune, Limited, a company that, on information and belief, is a subsidiary of AstraZeneca and developed durvalumab. On information and belief, AstraZeneca was aware of the MedImmune patent applications, and the citations to the EP878 patent, because, for example, they related to AstraZeneca's product IMFINZI. On information and belief, by at least as early as May 16,

2014, AstraZeneca was aware of the Honjo patent family and was aware the Honjo patent family included issued patents containing claims to methods of using anti-PD-L1 antibodies to treat tumors. On information and belief, AstraZeneca knew or should have known that the use of IMFINZI in methods of treating a tumor would infringe claims in the Honjo patent family at least as early as May 16, 2014.

58. Moreover, AstraZeneca has had knowledge of the '899 patent since the '899 patent issued because, on information and belief, AstraZeneca actively monitors its competitors' patent portfolios that could cover the IMFINZI product, and AstraZeneca and several of the Plaintiffs are direct competitors in the immunotherapy field, and more specifically, in the PD-1/PD-L1 antibody field. AstraZeneca markets or has marketed its anti-PD-L1 antibody durvalumab under the name IMFINZI for the treatment of several types of cancers, including cancers for which BMS, Squibb, and Ono market the anti-PD-1 antibody nivolumab under the name OPDIVO. On information and belief, AstraZeneca began marketing IMFINZI on May 1, 2017.

59. AstraZeneca has had knowledge of the '899 patent since the '899 patent issued because it is a large company that monitors its competitors' patent portfolios for patents that cover IMFINZI or the use of IMFINZI. On information and belief, AstraZeneca monitored BMS's patent portfolio because in or around May 2019, AstraZeneca approached BMS about licensing one or more patents in its PD-L1 patent portfolio. On information and belief, at least in connection with that outreach, AstraZeneca investigated BMS's portfolio of PD-L1-related patents and patent applications, which included rights under the '899 patent at that point. Therefore, AstraZeneca would have had knowledge of the '899 patent since at least that time. AstraZeneca also has had knowledge of the '899 patent since before this lawsuit because

AstraZeneca was aware of other companies that licensed BMS's PD-L1 patent estate so those companies could sell PD-L1 antibodies. By December of 2020, AstraZeneca was aware that BMS had entered a non-exclusive licensing agreement with Roche covering BMS's PD-L1 estate. Roche/Genentech, one of AstraZeneca's primary PD-L1 competitors, markets the anti-PD-L1 antibody TECENTRIQ. TECENTRIQ is an anti-PD-L1 antibody that was approved in 2016 for the treatment of urothelial carcinoma and non-small cell lung cancer, the same types of cancers that IMFINZI was later approved to treat. By December of 2020, BMS and AstraZeneca again discussed licensing BMS's PD-L1 patent estate.

60. AstraZeneca has had knowledge of the '899 patent since at least February 2019 when its in-house and outside counsel attended the trial in the Inventorship Action.

61. In the absence of actual knowledge, AstraZeneca has at least been willfully blind to the existence of the '899 patent since the '899 patent issued. AstraZeneca owns or controls numerous patents covering IMFINZI. AstraZeneca's subsidiary MedImmune, the company primarily responsible for AstraZeneca's development of IMFINZI, cited the EP878 patent, a European counterpart covering similar subject matter as the '899 Patent, in its own patent filings, including the '108 patent that covers IMFINZI. On information and belief, AstraZeneca was aware of the MedImmune patent applications, and the citations to the EP878 patent, because, for example, they related to AstraZeneca's product IMFINZI. AstraZeneca knew that BMS owned or licensed patents covering anti-PD-L1 antibodies, and their use, since at least 2019 based on previous licensing discussions between the parties and AstraZeneca's monitoring of the Inventorship Action. AstraZeneca knew that BMS licensed its PD-L1 estate to other companies that also market anti-PD-L1 antibodies to treat several of the same types of cancer as IMFINZI. AstraZeneca is a sophisticated company and, on information and belief, monitors the patent

estates of its competitors for patents that could cover the use of IMFINZI, particularly competitors, like BMS, who AstraZeneca has approached about licensing patents that cover IMFINZI. If AstraZeneca did not have actual knowledge of the '899 patent, it is because AstraZeneca took deliberate actions to avoid learning specifically about the '899 patent. If AstraZeneca did not have actual knowledge of the existence of the '899 patent, it is because AstraZeneca was willfully blind to the existence of the '899 patent.

62. AstraZeneca has known that the use of IMFINZI in patients to treat cancer infringes at least claims 1-9, 12, 16, 19-26, 29, 33, and 36-51 of the '899 patent since as early as August 2, 2016, when the '899 patent issued, but in any event, before receiving a copy of this complaint. AstraZeneca received a complaint in the 2017 Action alleging that the use of IMFINZI infringes many of these same claims of the '899 patent on July 31, 2017. IMFINZI is sold in a highly regulated market and AstraZeneca provided detailed prescribing information to users about how to administer and use IMFINZI to treat patients with cancer. IMFINZI's prescribing information states that IMFINZI blocks the interaction between PD-1 and PD-L1. Accordingly, once AstraZeneca knew of the '899 patent, AstraZeneca knew that the use of IMFINZI according to its prescribing information would infringe the '899 patent.

63. If AstraZeneca did not have actual knowledge that the use of IMFINZI in patients to treat cancer infringes at least claims 1-9, 12, 16, 19-26, 29, 33, and 36-51 of the '899 patent, then AstraZeneca was willfully blind to that fact. AstraZeneca conducted clinical trials to test whether IMFINZI could be used to treat cancer and presented such information to the United States Food and Drug Administration to show that IMFINZI was safe and effective for treating a tumor in cancer patients. AstraZeneca had actual knowledge of the '899 patent or was willfully blind to the existence of the '899 patent. AstraZeneca is a sophisticated company and upon

learning of a patent that covers the use of an anti-PD-L1 antibody to treat cancer, AstraZeneca subjectively believed that there was a high probability the use of IMFINZI would infringe the '899 patent. The '899 patent's independent claims do not require treatment of specific tumor types, but several of the dependent claims recite types of cancer that AstraZeneca was investigating and for which AstraZeneca ultimately received approval to market IMFINZI. Having knowledge of the '899 patent, the only way that AstraZeneca would not know that the use of IMFINZI infringed the '899 patent would be because AstraZeneca took deliberate action to avoid learning that the use of IMFINZI infringed the '899 patent.

64. AstraZeneca has contributed, and continues to contribute, to the infringement of at least claims 1-9, 12, 16, 19-26, 29, 33, and 36-51 of the '899 patent. IMFINZI is, and has been, especially made to inhibit an interaction between PD-1 and PD-L1 in order to treat a tumor. Thus, IMFINZI is especially made, and has been made, for use to infringe the claims of the '899 patent. Further, IMFINZI is only available, and has only been available, to purchase for use as a product to perform the claimed method and is not a staple article of commerce or suited for any substantial non-infringing use. For all of the reasons above, AstraZeneca knows, and has known since as early as the date the '899 patent issued, that IMFINZI is and has been especially made and/or especially adapted for use in infringing the '899 patent.

65. Through its prescribing information and promotional materials, including its websites and marketing materials, AstraZeneca has and continues to recommend and encourage healthcare providers to infringe the claims of the '899 patent. AstraZeneca has had and continues to have the specific intent to infringe and actively induce others to infringe the '899 patent.

66. Despite its knowledge that Plaintiffs owned and/or were licensed under patents that covered methods of treating cancer using an anti-PD-L1 antibody, AstraZeneca nonetheless sought approval for and launched its PD-L1 antibody IMFINZI for the treatment of cancer. On information and belief, AstraZeneca was aware no later than October 1, 2018, that inventor and plaintiff Tasuku Honjo was awarded the 2018 Nobel Prize in Physiology or Medicine for his work underlying the '899 Patent. On information and belief, AstraZeneca's counsel attended the trial in the 2019 Inventorship Action, a litigation over the proper inventorship of *inter alia* the '899 patent, on behalf of AstraZeneca. DFCI ultimately prevailed in the Inventorship Action. AstraZeneca's infringement of the '899 patent has been willful.

COUNT I: INFRINGEMENT OF U.S. PATENT NO. 9,402,899

67. Plaintiffs incorporate by reference paragraphs 1-66 as if fully set forth herein.

68. On information and belief, AstraZeneca is marketing, making, using, selling, offering for sale, and/or importing durvalumab in the United States for the treatment of cancer. On information and belief, durvalumab is being used for the treatment of cancer in the United States. As set forth above, AstraZeneca is thereby infringing at least claims 1-9, 12, 16, 19-26, 29, 33, and 36-51 of the '899 patent, including by actively inducing infringement under 35 U.S.C. § 271(b) and as a contributory infringer under 35 U.S.C. § 271(c).

69. On information and belief, AstraZeneca has been aware of the '899 patent since at least approximately August 2, 2016, when the USPTO issued the '899 patent and AstraZeneca's infringement is deliberate, egregious, willful, and in reckless disregard of valid patent claims of the '899 patent.

70. Plaintiffs have been and will continue to be injured by, and have been and will continue to suffer substantial damages as a result of, AstraZeneca's infringement.

71. This case is exceptional and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285.

JURY DEMAND

Under Federal Rule of Civil Procedure 38, Plaintiffs demand trial by jury of all issues so triable.

PRAYER FOR RELIEF

Wherefore, Plaintiffs respectfully request the following relief:

(a) entry of a judgment that Defendants infringe and will infringe the '899 patent;

(b) an award of damages sufficient to compensate Plaintiffs for infringement of the '899 patent, together with pre- and post-judgment interest and costs as fixed by the Court as provided by 35 U.S.C. § 284;

(c) entry of an order compelling Defendants to compensate Plaintiffs for any ongoing or future infringement of the '899 patent, in an amount and under terms appropriate for the circumstances;

(d) entry of an order that Defendants' infringement has been willful, and increased damages pursuant to 35 U.S.C. § 284;

(e) judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and an award to Plaintiffs of their reasonable attorney fees, costs, and expenses in this action pursuant to 35 U.S.C. § 285, Fed. R. Civ. P 54(d), and 28 U.S.C. § 1920; and

(f) such other relief as the Court may deem just and proper.

Dated: April 25, 2023

Respectfully submitted,

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